REMARKS/ARGUMENTS

At the outset, Applicants wish to thank Examiner Li and Examiner Brumback for their time and assistance during a telephonic interview with the undersigned, Mi Kim, Richard Pittner, a named inventor of the instant invention, and David Marsh, Amylin Pharmaceutical, Inc.'s representative, held on Nov. 10, 2004, as well as their continued assistance in the prosecution of the instant application.

On November 30, 2004, a non-final Office Action was mailed by the Patent Office vacating the Office Action mailed Sept. 20, 2004, and withdrawing or replacing all previous rejections of record. Based, in part, on the discussions with the Examiners, Applicants submit the instant Response.

Status of the Claims

Claims 1, 8, and 33-54 were pending. In the instant Response, Applicants have amended claims 1, 8, 34-41, 43-44, 46, and 52-53. With the entry of the present amendment, claims 1, 8, 33-54 are currently pending in the application.

Support for the amendments to the claims directed to the subject population can be found throughout the specification in general. The specification is directed to the discovery of novel actions of PYY and PYY agonists and uses based upon those discoveries. Accordingly, one of skill in the art would comprehend that implicit to the claimed methods is the understanding that the methods are to be performed on a subject who desires, as deemed by the subject or administrator, to experience the action stated in the claims. Thus, it is implicit that with the discovery of the novel actions (the invention) there is recognition of a subject that would desire the action (or that can benefit from it). Support for the amendments to the claims directed to the subject population being human can be found throughout the specification and at least at page 14, lines 28-31. Support for the addition of "PYY agonist analog" to clarify the PYY agonist in claim 53 can be found at least at page 6, lines 5-13; and page 11, lines 2-7. Applicants submit that the amendments were made solely to expedite prosecution and reserve the right to prosecute

any subject matter not now included in the claims in a future application. Applicants submit that no new matter has been introduced by the instant amendment.

Issue under 35 U.S.C. §112, first paragraph

Claims 1, 8, 33-54 are rejected under 35 U.S.C. 112, first paragraph, as the Patent Office has alleged that while the specification enables claims for a method of peripherally administering an effective amount of PYY or PYY(3-36) to a subject, it does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims. Applicants respectfully traverse for the reasons stated below.

The Patent Office alleges there are two key issues. First, the Patent Office notes that claims 8, 33-36, 43-52, and 54 are not limited to peripherally administered PYY or PYY agonists. In order to advance prosecution of the instant application, Applicants have amended claims 8, 33-36, 43-52, and 54 to recite to peripheral, in contrast to central, administration.

Second, the Patent Office points to pages 5 and 6 as describing a PYY agonist. However, in spite of this description of PYY agonists, the Patent Office alleges that the claims are drawn to a method comprising administration of a genus of structurally undefined PYY agonists. Applicants, however, submit that PYY agonists are not undefined and respectfully point out that the genus is viewed from the perspective of one of ordinary skill in the art.

The specification describes PYY agonists in terms of function and structure. For example, the specification states that PYY agonists may have activity in any of the assays described in the specification, e.g., food intake, gastric emptying, pancreatic secretion or weight loss, as well as having particular binding affinities. Moreover, the specification describes PYY agonists as having structural similar to PYY (but specifically excludes pancreatic polypeptide (PP) as a PYY agonist, see page 5, line 30), and which also includes derivatives, extended or truncated molecules, substituted molecules, and modified molecules of the same. This description is provided against a backdrop of what was known in that art at the time of filing, at

the least the work described in US Pat. Nos. 5,574,010; 5,604,203; 5,696,093; and 6,046,167. These patents describe PYY agonists. Accordingly, the skilled artisan would read the newly discovered uses of PYY and PYY agonists disclosed in the present application in view of the work in the art about PYY and PYY agonists. In this manner, one of skill in the art would understand that the scope of the claimed invention is directed to the novel uses of PYY and PYY agonists, and not directed to the use of any particular PYY agonist in the methods of the invention. Applicants, therefore, submit that one of ordinary skill in the relevant art would be able to comprehend the scope of PYY agonists as used in the instant claims. Similarly, one of skill in the art would understand that the claims are not directed to specific agonists of GLP-1, exendin, or Amylin, but only that these compounds, which are known in the art can be useful in the claimed methods of the invention.

The Patent Office points to PYY(6-36) and PYY(13-36) as allegedly being unable to inhibit gastric acid secretion or pancreatic exocrine section. The Patent Office reasons that these PYY agonists would, therefore, not work in the same manner as that of PYY. Applicants submit that while PYY(6-36) and PYY(13-36) may not possess certain functions of PYY, they do possess other functions of PYY, such as Y receptor binding, making them PYY agonists. Applicants submit that it is not any one particular function of PYY that makes them useful to the claimed methods. These functions are merely one way to describe the PYY agonists contemplated to be within the scope of the invention.

Applicants submit that it is not essential to the methods that a PYY agonist has all the same characteristics as PYY. In fact, some PYY agonist, such as PYY(3-36), may not have all the characteristics of PYY, making them a superior compound in the claimed invention. For example, Applicants submit that PYY(3-36) does not appear to have the hypertensive effect reported for PYY. The claimed invention of the present application is based upon Applicants' discovery that PYY and PYY agonists can elicit the actions described in the claimed methods. It would not have been undue experimentation for one of ordinary skill in the art, based upon the relevant art and the assays described in the instant disclosure, to determine the PYY agonists that

may be useful in the invention. As an aside, Applicants submit that a valid claim may include inoperative embodiments.

Claims 1, 8, 33-46, and 48-54 are rejected under 35 U.S.C. §112, first paragraph for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one of skill in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse.

As discussed above, Applicants submit that the specification describes the function and structure of PYY and PYY agonists. This description of PYY agonists must also be read in light of what one of ordinary skill would know about the prior art. Knowledge at the time of filing of the application includes that which is described in US Pat. Nos. 5,574,010; 5,604,203; 5,696,093; and 6,046,167. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d at 1384, 231 USPQ at 94.

The Patent Office relies upon *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, as stating "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention." The Patent Office alleges that the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of the PYY agonists and therefore conception is not achieved until reduction to practice has occurred. Applicants respectfully disagree. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. See, e.g., *Vas-Cath*, 935 F.2d at 1563, 19 USPQ2d at 1116; *Martin v. Johnson*, 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972) (stating "the description need not be in *ipsis verbis* [i.e., "in the same words"] to be sufficient"). While the standards may be different if the invention were drawn to composition claims of PYY agonists, here, where the invention is drawn to a novel method of using PYY agonists, the description provided in the specification as well as the PYY

agonists that were known at the time of filing would have provided the skilled artisan with reasonable clarity as to the scope of the claimed invention.

In light of the remarks set forth, Applicants respectfully request reconsideration and withdrawal of the rejection to claims 1, 8, 33-46, and 48-54 based upon 35 U.S.C. §112, first paragraph.

Issues under 35 U.S.C.§112, second paragraph

Claims 1, 8, 33-37, 42, 47, 51, 52, and 54 are rejected under 35 U.S.C. §112, second paragraph for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Patent Office alleges that it is unclear whether the term "a PYY" recited in the claims is intended to refer to only SEQ ID NO:2 or both SEQ ID NO:2 and PYY(3-36). Applicants submit that the claims refer to "a PYY" as including species variations of human PYY, including e.g., murine, hamster, chicken, bovine, rat, and dog, see page 5, lines 22-24 of the specification. The PYY agonist PYY(3-36) is identified as SEQ ID NO:3. Accordingly, in the claims, "a PYY" includes SEQ ID NO:2 and "PYY agonists" include PYY(3-36).

The Patent Office alleges that claim 42 is indefinite because it recites "wherein the PYY agonist has a higher affinity for the Y5 receptor over the Y1 receptor" and it is unclear to the Patent Office how the Y5 receptor is related to the Y2 receptor that is recited in claim 38 from which claim 42 depends. Applicants respectfully submit that the claim is not indefinite. The ability of any one peptide to bind to a Y receptor is independent of its ability to bind to another Y receptor. Accordingly, the PYY agonist of claim 42 has a higher affinity for the Y5 receptor over the Y1 receptor and a higher affinity for the Y2 receptor over the Y1 receptor. However, the PYY agonist of claim 42 may have a higher affinity or a lower affinity for binding the Y2 receptor over the Y5 receptor.

In light of the above remarks, Applicants respectfully request reconsideration and withdrawal of the rejection to claims 1, 8, 33-37, 42, 47, 51, 52, and 54 based upon 35 U.S.C. §112, second paragraph.

Issues under 35 U.S.C. §102(b)

Yoshinaga et al. (Am. J. Physiol. 263:G695-701, 1992)

Claims 1, 8, 33-43, 47-49, and 52-54 are rejected under 35 U.S.C. 102(b) for alleged being anticipated by Yoshinaga. Applicants respectfully traverse.

Claims 1, 8, 33-43, 47-49, and 52-54 have been amended to clarify the scope of the claims. The method claims now clarify the subject population. Applicants submit that claims 1, 8, 33-42, 47-49, and 52-54 are not narrowed by the amendments as the subject population was always implied, *i.e.,* the methods were always directed to a population who one would desire to have experience the methods. Claim 43 and claims dependent thereon are amended to be directed to a human subject.

Seen in this light, Yoshinaga does not inherently anticipate the claimed invention. Yoshinaga reports the effects of PYY and PYY(3-36) on pancreatic exocrine and gastric acid output in dogs. Yoshinaga, however, does not teach or imply that PYY or PYY(3-36) has an effect on caloric efficiency, nutrient availability, appetite, food intake, or weight. Moreover, Yoshinaga does not teach administration to humans. Accordingly, Yoshinaga cannot render unpatentable by inherency the claimed patient population, humans and/or those that would benefit from affecting caloric efficiency, nutrient availability, appetite, food intake, or weight. Thus, Yoshinaga's description does not inherently perform each and every element of the claimed invention. Inherency requires that an element must necessarily be present. Because the subject population of Yoshinaga would not necessarily include humans or subjects that may benefit from affecting caloric efficiency, nutrient availability, appetite, food intake, or weight, Yoshinaga does not inherently render the claimed invention unpatentable.

Morley et al. (Life Sci. 41:2157-2165, 1987)

Claims 1, 8, 33-44, 46-50, and 52-54 are rejected under 35 U.S.C. §102(b) for allegedly being anticipated by Morley. Applicants respectfully traverse.

Morley, when viewed as a whole, does not teach a method of reducing body weight by peripherally administering PYY. Applicants submit that one of ordinary skill in the art, reading Morley, would not believe that the described experiment supported its conclusion.

The ordinary, skilled artisan is someone with a critical eye who is familiar with scientific experiments and how to analyze data. Thus, when reading Morley, the skilled artisan would quickly note that the control mice gained weight in all the experiments except that of PYY administration. Putting the PYY experiment aside for the moment, it would, therefore, be the normal condition that all of Morley's control mice will gain weight. However, in Morley, the only control mice that did not gain weight were in the PYY experiment. The sole reason experiments have controls is to ensure that the experiments are run properly and that the results can be relied upon. Conversely, when controls fail, it means that the results of the experiment are not reliable. Because the control failed in the PYY experiment, Applicants submit that one of ordinary skill in the art would consider Morley's results, and its conclusion based upon those results, as being unreliable.

It is also curious to note that the magnitude of the weight difference between the control mice and PYY-administered mice is similar to the magnitude of the weight difference between control mice and mice administered compounds Morley reports as having no effect on weight. For example, the magnitude of difference between control and PYY-treated mice is about 1 gram (Figure 5A). The magnitude of difference between control and CCK-8S-treated mice and control and bombesin-treated mice are also about 1 gram, (Figures 3A and 3B, respectively). Morley, however, concludes that CCK-8S and bombesin did not cause significant weight loss (page 2161, line after the figure legend), but that PYY did. Applicants submit that one of ordinary skill in the

art would be further disinclined to give any weight to Morley's conclusion based upon this inconsistency.

Moreover, the skilled artisan would be even more disinclined to believe Morley's unsupported conclusion based upon his/her knowledge of the art. Around the time Morley was published, it was generally believed that NPY and PYY were orexigenic agents (see for example, Morley et al. Peptide YY (PYY), a potent orexigenic agent, Brain Res. 1985 Aug 19;341(1):200-3). This belief was so prevailing that commercial companies spent much time, effort, and resources in searching for an antagonist of the known Y receptors for the treatment of eating disorders and obesity, see for example, Exhibit documents WO 94/00486, WO 97/20823, EP 0889034, WO 98/35957, WO 01/02379, and US Pat. 6,127,414. These references clearly show that the field, at the time of Applicants' filing, considered antagonism to be the approach to treating eating disorders and obesity, among other disorders. Accordingly, Applicants submit that the instant claims drawn to PYY and PYY agonists are not anticipated by Morley, as Morley does not provide credible evidence for one of ordinary skill in the art to go against the prevailing beliefs of the time.

Furthermore, Morley cannot anticipate claims 8, 34-38, 43, 44, and 46, as well as claims dependent therefrom, as it teaches away from the claimed invention. In one aspect of the invention, these claims relate to reducing food intake, reducing appetite, or reducing nutrient availability. Morley teaches away because it states that PYY did not alter food intake (Figure 5B) (see page 2161, lines 9-10 from the bottom of Morley). Thus, Morley does not teach that PYY alters food intake or has an effect on appetite or nutrient availability and, therefore, cannot anticipate claims 8, 34-38, 43, 44, and 46. Neither can Morley anticipate claims 38-41 and claims dependent therefrom as Morley does not teach the use of PYY agonists with the binding profile of claims 38-41.

Okada et al. (*The Endocrine Society 75th Annual Meeting Program & Abstract*, page 180, Abstract 520B, 1993

Claims 1, 8, 33-44, 46-50, and 52-54 are rejected under 35 U.S.C. § 102(b) for allegedly being anticipated by Okada et al. Applicants respectfully traverse.

Okada describes an experiment where rats were administered PYY. Okada reports that the PYY-administered rats reduced their intake of high fat chow. However, Applicants submit that Okada does not teach that PYY had an effect on caloric efficiency, nutrient availability, appetite and food intake of non-high fat foods, or weight. Accordingly, Okada cannot inherently anticipate the use of PYY and PYY agonists for affecting caloric efficiency, nutrient availability, appetite and food intake of non-high fat foods, and weight. Claims 43-46, and claims dependent thereon, are directed to humans and, therefore, Okada cannot inherently anticipate these claims.

Moreover, the doses used by Okada are in the amount of 1, 10, 20, and 40 nmol. Assuming that the assumptions made in the Office Action are correct and the lowest dose given to the rats was about 14 to 22 μg/kg, the doses would have been much too high to anticipate the doses to humans in claims 43-46. For example, 14 μg/kg for an average human of 50 to 70 kg, would be equivalent to at least 700 μg of PYY per day. Finally, Applicants submit that the range of "about 0.1 μg/kg to 10 μg/kg per day" in claims 44 and 46 are less than 14 μg/kg. Thus, Okada cannot read on these claims.

In light of the remarks provided above directed to Yoshinaga, Morley, and Okada, Applicants submit that the present claims are patentable over Yoshinaga, Morley, and Okada, and respectfully requests reconsideration and withdrawal of the rejections based upon 35 U.S.C. 102.

Issues under 35 U.S.C.§103(a)

Claim 45 is rejected under 35 U.S.C. §103(a) for allegedly being unpatentable over Okada. The Patent Office alleges that because Okada described an experiment using 1, 10, 20,

and 40 nmol of PYY in rats and hypothesized that PYY may be a satiety factor for fat meal, the administration of administering PYY to a human to reduce appetite would have been obvious.

Applicants respectfully disagree. The doses used by Okada in rats would not have provided one of ordinary skill in the art with information to contemplate the doses claimed for use in humans. For instance, Okada gave about 4.3, 43, 86, and 172 μg of PYY to rats we assume to be about 200 to 300 g. An average human is about 50 kg. In Okada, a minimum daily dose would be about 14 μg/kg for an average rat. In claim 45, the minimum daily dose would be about 0.1 μg/kg (more than 100 fold less), with a maximum daily dose of about 2 μg/kg for an average human. It would not have been a logical and obvious step for one of skill in the art to have equated the doses given to rats in Okada with the doses in claim 45 directed to humans, as Okada does not teach or suggest how those doses would correlate to use in humans. Applicants are not aware of any teachings that would suggest that amounts given to rats in Okada would provide a reasonable expectation of success in humans. Moreover, claim 45 is directed to reducing appetite in humans. It is unclear from the Okada reference that appetite was reduced rather than another effect such as food preference for non-high fat foods. Accordingly, Applicants submit that Okada does not render obvious claim 45.

Claim 51 is rejected under 35 U.S.C. §103(a) for allegedly being unpatentable over Okada in view of Naslund et al. (Int. J. Obes. Relat. Metab. Disord. 23:304-311, 1999). The Patent Office alleges that Naslund teaches intravenous infusion of GLP-1 suppresses energy intake and appetite in obese men and, therefore, it would have been obvious to modify the method of Okada to administer GLP-1. Applicants respectfully disagree.

Applicants submit that Naslund cannot cure the deficiency of Okada, for the reasons provided above, to render claims 1, 8, 34 to 41, 43 to 46, and 52 to 53 unpatentable. Because claims 1, 8, 34 to 41, 43 to 46, and 52 to 53 are patentable over Okada and Naslund, claim 51 is patentable as well.

Claim 51 is rejected under 35 U.S.C. §103(a) for allegedly being unpatentable over Morley in view of Naslund et al. (Int. J. Obes. Relat. Metab. Disord. 23:304-311, 1999). The Patent Office alleges that Naslund teaches intravenous infusion of GLP-1 suppresses energy intake and appetite in obese men and, therefore, it would have been obvious to modify the method of Morley to administer GLP-1. Applicants respectfully disagree.

Applicants submit that Naslund cannot cure the deficiency of Morley, for the reasons provided above, to render claims 1, 8, 33-44, 46-50, and 52-54 unpatentable. Because claims 1, 8, 33-44, 46-50, 52-54 are patentable over Morley and Naslund, claim 51 is patentable as well.

CONCLUSION

Applicants respectfully submit that the claims are now in condition for allowance and request that a timely Notice of Allowance be issued in this case. The Examiner is encouraged to call the undersigned attorney to discuss any issues related to the prosecution of the instant application.

Applicants believe that with the payment of an extension of time fee no additional fee is necessitated by the present paper. However, in the event any other fee is due or an amount is to be credited in connection with the instant response, Applicants authorize the Commissioner of Patents to debit or credit Deposit Account No. 010535.

Respectfully submitted,

3/28/2005

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